- The HIV/STD/TB/Hepatitis Program in the Division of Disease Control is starting a series of Lunch and Learn Webinars for health-care professionals.
- Each month a new topic will be held from 12:00 p.m. to 1:00 p.m. CST on the fourth Wednesday of the month.
- Nursing education credits will be available for these presentations. Registration and schedule of topics are available at: http://www.ndhealth.gov/HIV/events.htm
- The schedule of topics will be updated as they become available. The presentations will also be archived and available on the above website.

TB 101

Dee Pritschet, TB Controller
North Dakota Department of Health
May 28, 2014

- This presentation will highlight information about tuberculosis (TB) and include TB information specific to North Dakota

Objectives

Participants will be able to:

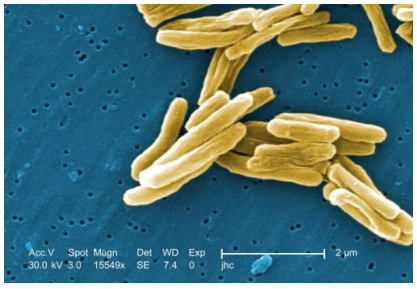
- 1) describe the cause of tuberculosis (TB), progression and management
- 2) testing and treatment options
- 3) populations at risk for TB in North Dakota

Tuberculosis (TB)

- TB is caused by a bacteria – Mycobacterium tuberculosis
- Other names for TB are:
  - consumption
  - wasting disease
  - the white plague
  - Koch's disease

History of TB Disease

- This organism has been documented as early as 1000 BC
- Until mid-1800s, many believed TB was hereditary
- 1865 Jean Antoine-Villemin proved TB was contagious
- 1882 Robert Koch discovered *M. tuberculosis,* the bacterium that causes TB



- Before TB antibiotics, many patients were sent to sanitariums
- Patients followed a regimen of bed rest, open air, and sunshine
- TB patients who could not afford sanatoriums often died at home


San Haven Sanatorium – Dunseith, ND

Ghosts of North Dakota – San Haven Sanatorium

http://www.ghostsofnorthdakota.com/2011/01/12san-haven-sanatorium/

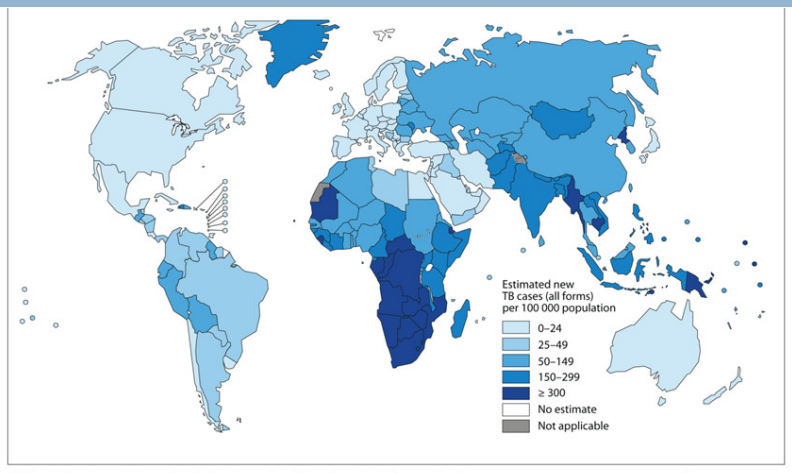
Global TB

- 1/3 of the world's population is infected with TB
- 8 million people develop active TB each year
- TB kills more young women than any other disease
- TB kills more than 5,000 people every day
- 2.3 million die each year

Tuberculosis Disease

- In 2012, there were an estimated 450,000 cases of multi-drug (MDR) TB worldwide
- Children account for 500,000 new cases annually and 75,000 will die of TB disease
- Hundreds of thousands of children will become orphans this year due to TB
- 10% of people with TB infection will progress to active TB in their life; 5% in the first 2 years of infection and 5% at some time over their lifespan

Estimated tuberculosis incidence rates, 2011



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Source: *Global Tuberculosis Report 2012*. WHO, 2012.

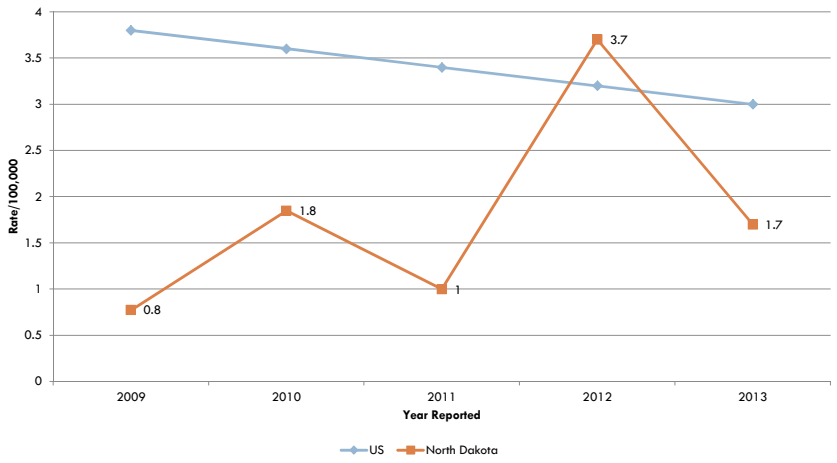
World Health Organization

TB Disease in the United States

- 64.6% of the cases of active TB in the US in 2013 were foreign born persons
- In order to control the spread of TB, one must identify those that have been infected
- Once identified those same individuals need to be treated to reduce their risk of developing active disease

TB Case Rates, United States, 2012

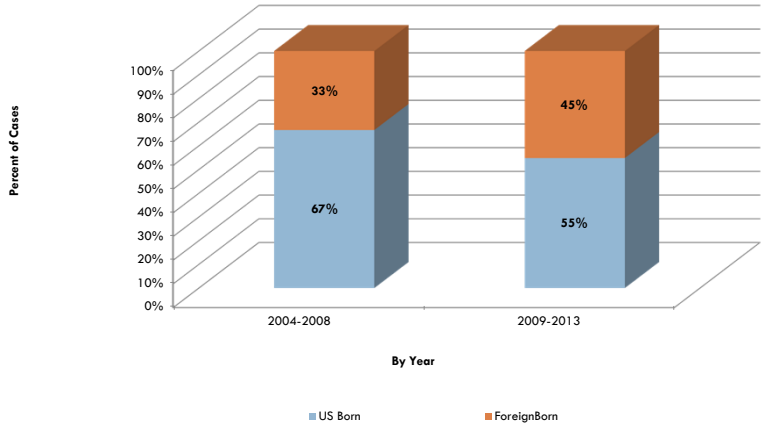
United States and North Dakota TB Disease Rates, 2009 - 2013



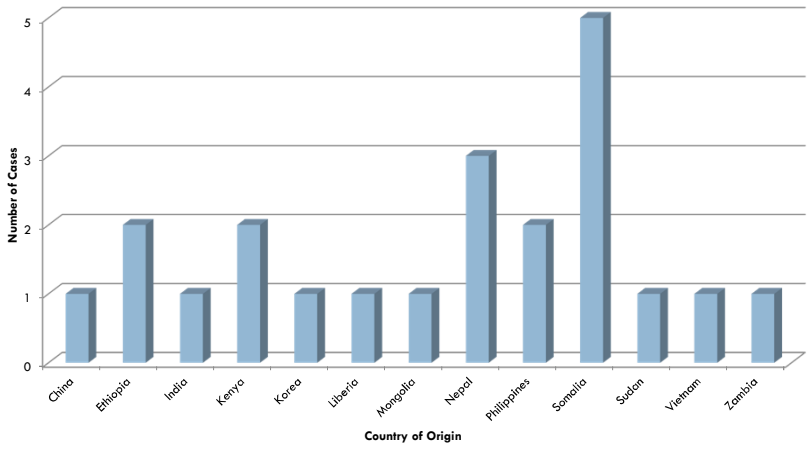
Who is at Greatest Risk for developing disease?

- Contacts to known TB cases
- Persons with HIV or other immunosuppressed diseases
- Persons from countries where TB is common (Latin America, the Caribbean, Asia, Africa, Eastern Europe and Russia)
- People who work in or live in facilities where TB is common: homeless shelters, correctional facilities, hospitals and clinics, nursing homes

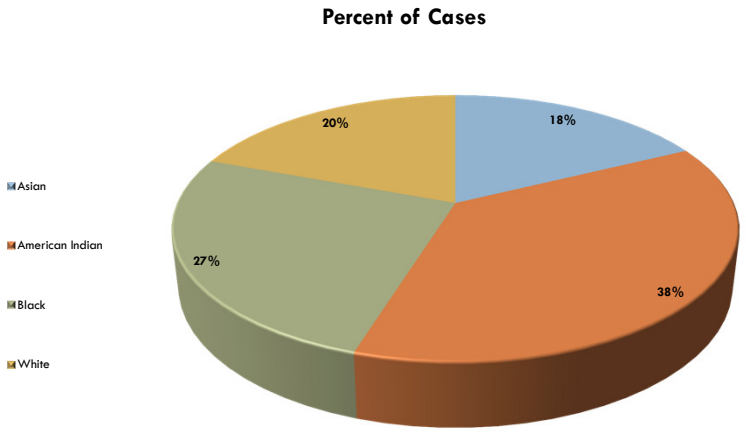
Percentage of TB Cases
U.S.-Born and Foreign-Born in North Dakota, 2009 - 2013



Countries of Origin for Active Cases in North Dakota, 2009 - 2013



Tuberculosis Cases by Race in North Dakota, 2009 - 2013



Additional Risk Factors

- Conversion in TB test
- Low body weight or malnourished
- Radiological evidence of old healed TB
- Abuses alcohol or other illegal drugs
- Incomplete LTBI treatment
- Medical Conditions such as
  - Diabetes
  - Silicosis
  - Organ transplantation
  - Chronic Renal Failure
  - Cancers of the head and neck
  - Gastrectomy or jejunoileal bypass
  - Conditions that require prolonged use of corticosteroids or other immunosuppressive agents (TNF-alpha antagonists, chemotherapy)

Mycobacteria

Mycobacteria that cause TB disease

- *Mycobacterium tuberculosis*
- *Mycobacterium bovis*
- *Mycobacterium africanum*
- *Mycobacterium microti*
- *Mycobacterium canetti*

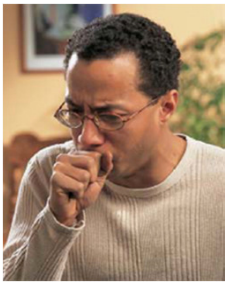
In the United States, most TB is caused by *Mycobacterium tuberculosis*

Mycobacteria that do not cause TB disease

- *Mycobacterium avium*
- *Mycobacterium fortitum*
- *Mycobacterium chelone*
- *Mycobacterium gordonae*
- *Mycobacterium kansaii*

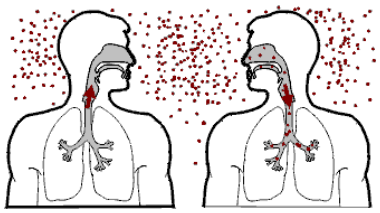
How is TB Spread?

- TB is spread person to person through the air via droplet nuclei
- *M. tuberculosis* may be expelled when an infectious person:
  - Coughs
  - Sneezes
  - Speaks
  - Sings
- Transmission occurs when another person inhales droplet nuclei



Transmission

- Transmitted through airborne droplets
- Large infectious dose needed
- Must be in close contact



Pathogenesis

- Infection begins when the inhaled droplets reach the alveoli of lungs
- Tubercle bacilli multiply
- A number of tubercle bacilli enter the bloodstream and spread throughout the body (lungs, kidneys, brain, bone)
- Within 2-10 weeks, the immune system produces an immune response which encapsulates the bacteria, and is detectable with a TST or IGRA blood test

Risk of Infection

- How infectious is the person with TB
- Length of exposure
- Environment in which transmission occurs
  - Close proximity
  - Indoors, Outdoors

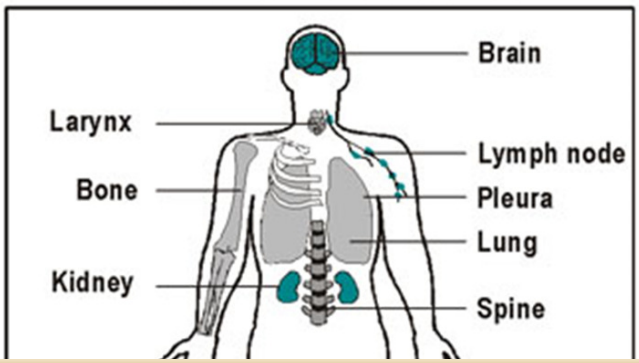
Likelihood of Developing TB Disease

- Once infected with tubercle bacilli
  - 10% life time chance that TB disease will develop
    - Half the risk within the first 2 years
    - Gradually decreasing risk after the first 2 years
  - 90% chance of never developing the disease
  - Other personal health factors can influence risk
    - HIV infection - single highest risk for progress to active disease, at 10% risk annually
    - Diabetes – 30% risk over lifetime

Sites of TB Disease

- Pulmonary TB – lungs, 80-85% of TB cases
- Extra-pulmonary TB– outside of the lungs
  - Can occur anywhere in body
  - Typical sites include larynx, lymph nodes, the pleura, brain, kidneys, bones, or joints
  - Usually not infectious – always rule out pulmonary!
  - Laryngeal TB is extremely contagious – hoarseness
  - Found more often in those that are HIV infected, immunosuppressed person or young children
- Miliary TB – carried to all parts of the body, through the bloodstream

Bacilli may reach any part of the body, but common sites include:

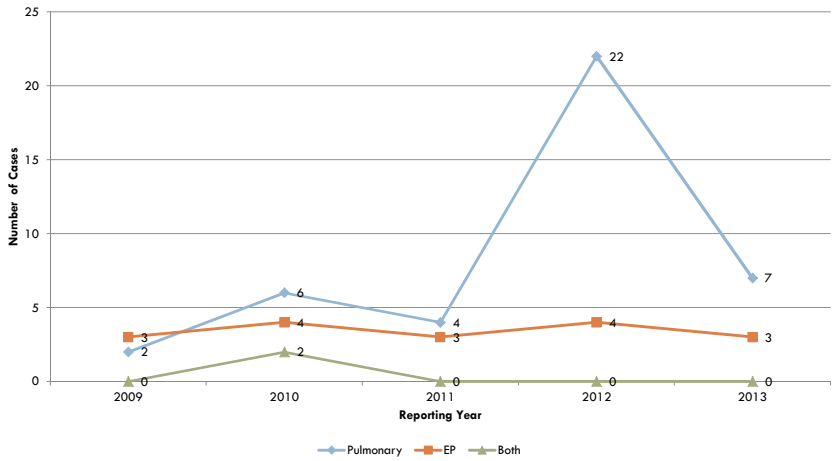


Sites of TB Disease

TB is primarily pulmonary

TB can also be present in the bones, other organs

Types of TB Disease in North Dakota, 2009 - 2013



Why Screen for TB

- Tuberculosis is one of the world's deadliest diseases
- Once identified, treatment can begin
- Once treatment begins, the spread of disease can be halted

Diagnosis of TB Infection /Disease

- TST
- IGRA
  - QFT
  - T-Spot
- CXR
- Culture

Active Disease vs. Latent Infection

Active TB Disease

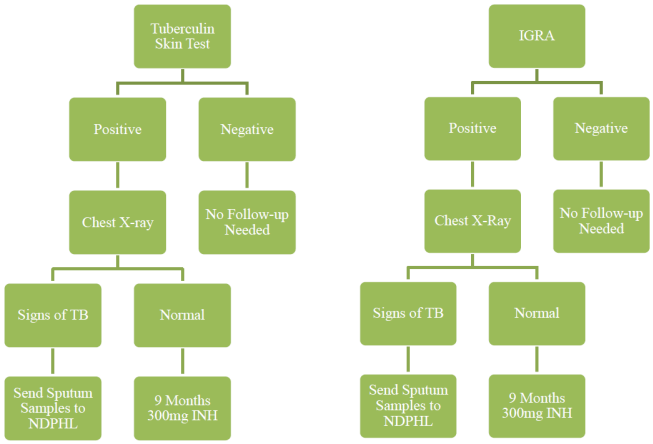
- Positive TST or IGRA
- Cough, fever, unexplained weight loss, chest pain, fatigue, loss of appetite
- Abnormal CXR
- Positive sputum smears
- Positive sputum cultures
- Infectious prior to treatment

May have a negative sputum smear &/or culture

Latent TB Infection (LTBI)

- Positive TST or IGRA
- Normal CXR
- Negative sputum smear
- Negative sputum culture
- Not infectious

TB Screen Algorithm



Tuberculin Skin Testing

- In 1890, Robert Koch announced a cure for TB, 8 years after discovering the cause of TB
- Cure consisted of subcutaneous doses of tuberculin
- Subsequently found to be ineffective
- Became a diagnostic test for TB infection

Who can Receive a TST

- Almost everyone can receive a TST, including: infants
- Children
- Pregnant women
- People living with HIV
- People who have had a BCG shot

*People who had a severe reaction to a previous TST ***should not*** receive another TST

Mantoux Skin Testing

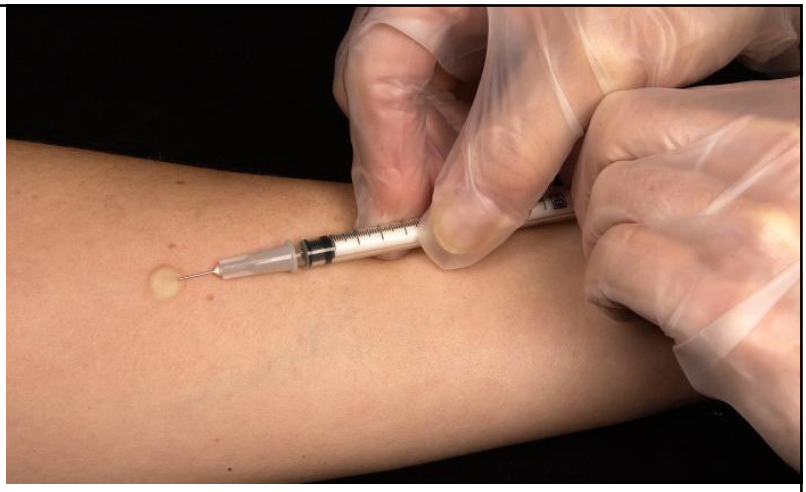
Developed by Charles Mantoux in 1908

The standard tuberculin skin test

Two Purified Protein Derivative (PPD) antigen products licensed by the FDA

- Tubersol
- Aplisol

If at all possible do not switch between the two brands of tuberculin antigen



How to Perform the Tuberculin Skin Test

Inject intradermally 0.1 ml of 5 TU (Purified Protein Derivative) PPD tuberculin

Produce a wheal 6 mm to 10 mm in diameter

Factors that May Affect the Skin Test Reaction

False Positive

- Non-tuberculous mycobacteria BCG vaccination
- BCG vaccination

False Negative

- Anergy
- Recent TB infection
- Very young age (<6 months old)
- Live-virus vaccination
- Overwhelming TB disease or other infection

BCG Vaccination

- Bacillus of Calmette and Guerin
- First officially used as a TB vaccine in 1921
- Poor efficacy but believed to be useful in some foreign countries to prevent TB disease in young children and infants
- Not recommended in the United States
  - Low risk of infection with M. tuberculosis
  - Variable effectiveness of BCG
  - Interpretation of tuberculin skin test result complicated by BCG

Storage and Handling of PPD

- Date and initial when vial is opened
- Discard 30 days after opening
- Draw up just prior to injection
- Store at 35-46 degrees Fahrenheit in a refrigerator or cooler with ice packs and keep out of direct light (antigen is sensitive to light and heat; these elements can affect antigen's stability and potency)

Reading the TST

- Must be read 48-72 hours after the test is placed
- Measure the induration in mm – not erythema
- If test is not read by 72 hours, repeat the test – no waiting time is required

Classification of the TB Skin Test

An **induration of 5 or more millimeters** is considered positive in	An **induration of 10 or more millimeters** is considered positive in	An **induration of 15 or more millimeters** is considered positive in any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.
-HIV-infected persons -A recent contact of a person with TB disease -Persons with fibrotic changes on chest radiograph consistent with prior TB -Patients with organ transplants -Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)	-Recent immigrants (< 5 years) from high-prevalence countries -Injection drug users -Residents and employees of high-risk congregate settings -Mycobacteriology laboratory personnel -Persons with clinical conditions that place them at high risk -Children < 4 years of age - Infants, children, and adolescents exposed to adults in high-risk categories	

Source: Centers for Disease Control and Prevention

Two-Step Testing

- Done to establish a baseline for those that will be retested periodically
  - If first test is positive, consider person infected
  - If first test is negative, give 2nd test 1-3 weeks later
  - If second test is positive, consider person infected
  - If second test is negative, consider the person uninfected

Key Definitions

Reactor

- An individual with a positive skin test reaction (size interpreted as "positive" based on risk factors) with no clear documentation or history of being skin tested in the last two years

Convertor

- Any individual with a negative skin test documented as baseline but who developed positive reaction with increase in reaction size of >/= 10 mm within the past two years or a change from negative to positive on an IGRA

IGRA

Interferon Gamma Release Assay (IGRA) measure the cell-mediated response to specific TB antigen in whole blood. WBC's in TB infected person release INF-g when mixed with antigens derived from Mycobacteria Tuberculosis (MTB).

Currently there are two IGRA's in use: Quantiferon (Cellestis) and T-Spot (Oxford)

Quantiferon

T-Spot

Advantages of IGRA's

Advantages of IGRA's

- Requires a single patient visit
- Results not subject to ready bias and error
- Greater sensitivity and specificity – not affected by BCG or most nontuberculous mycobacteria
- Results are usually available within 24-48 hours
- Does not "boost" responses measured by subsequent tests as a TST may

Disadvantages of IGRA's

- More costly than a TST*
- Not recommended for use in children </= 5 years of age
- Blood must be processed in 8-30 hours
- Can have false positive, false negative and indeterminate test results

Factors that May Affect the IGRA Result

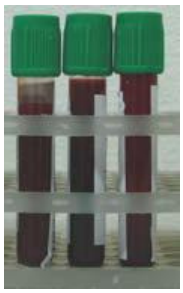
False Positive

- Issues with collection of tubes
- Improper collection, transport of tubes, running or interpretation of the result

False Negative

- Delay in incubation
- Improper collection, transport of tubes, running or interpretation or the result

T-Spot



- T-Spot uses 1 lithium or sodium heparin tube (EDTA is not recommended)
- Requires differing amounts of blood:
  - Adults and Children over 9 years old – 6 ml
  - Children 2-9 years old - 4 ml
  - Children up to 2 years old – 2 ml

  NOTE if patient is HIV positive, collect two tubes
- Whole blood tubes must be stored at room temperature until packaged for transport

Interpretation of Results

Interferon-gamma is captured and presented as spots from T cells sensitized to Mycobacterium tuberculosis antigens.

There are 4 panels used. Results are interpreted by subtracting the spot count in the negative (NIL) control from the spot count in Panels A and B. The 4th panel is the antigen panel or positive control. Results are reported as positive, negative, borderline and indeterminate.

QFT

QFT-GIT requires 3 tubes provided by the lab
Each tube is designed to allow only 1 ml of blood to be collected

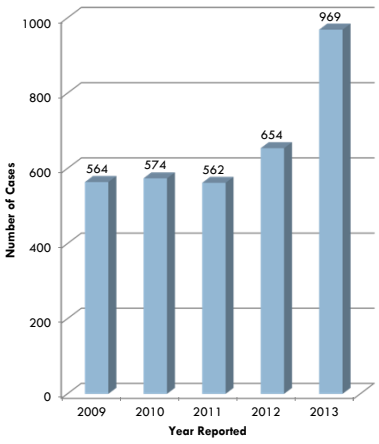
Gray – Negative Control or Nil – "background noise"
Red – Antigen – Response of the test
Purple – Positive Control or Mitogen – shows immune status and correct handling and incubation of the tubes

Will receive a numeric as well as a positive, negative or indeterminate result.
The result is based on IFN-g (Interferon gamma) concentation
Positive - >/= 0.35
Negative < 0.35
Indeterminate - <0.35 or >/= 0.35 if Nil > 8.0 and any result in Mitogen tube
Or any result in antigen and mitogen with > 8.0 in Nil

LTBI Treatment

- To prevent active TB disease, treatment for latent TB is very important
- 9 months isoniazid (INH) – 270 doses
  - May be given daily or twice a week
- Rifampin (RIF) – 4 months
- Isoniazid-Rifapentine - 12 week course, must be given DOT
- In situations where RIF cannot be used (HIV-infected persons receiving protease inhibitors – rifabutin may be substituted

Number of LTBI Cases, 2009 - 2013



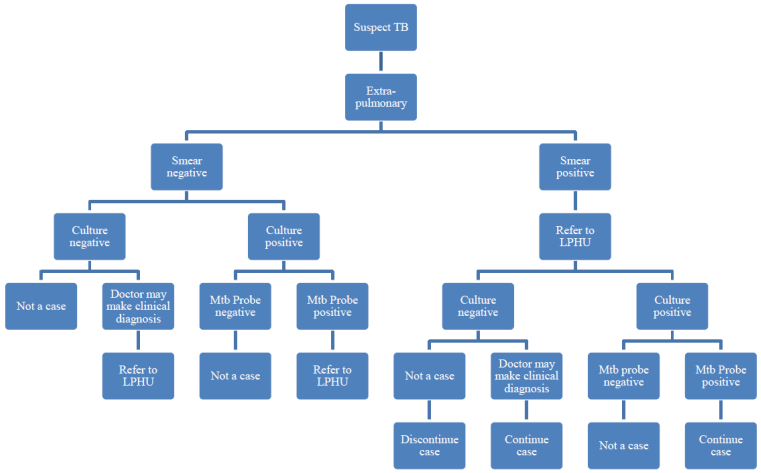
Why are we seeing an increase?

- More cases?
- Better reporting?
- More testing?
- TB outbreak in Grand Forks?

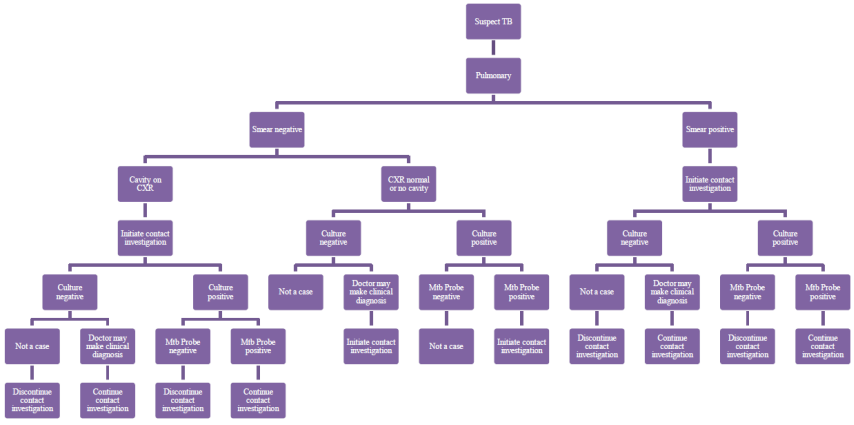
Chest X-Ray

- Check for lung abnormalities suggestive of TB disease
- Typical findings may include cavities, infiltrates, effusions, opacities
- A chest x-ray does not confirm TB disease
- A chest x-ray does not rule out active TB in immune compromised individuals and children

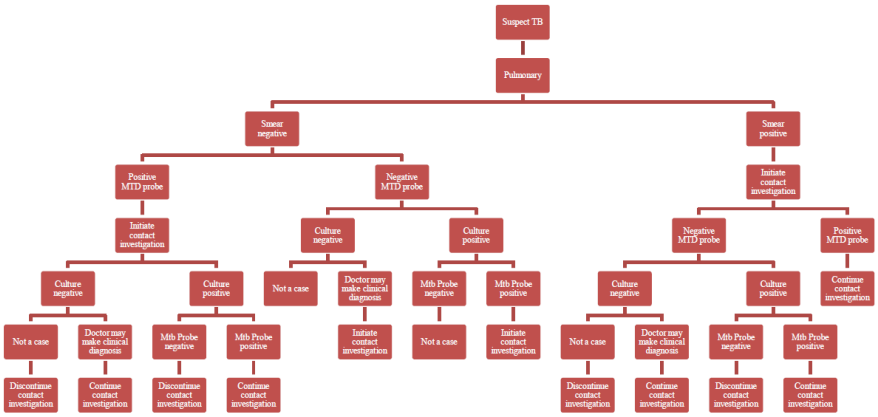
Suspect Extra-Pulmonary TB: AFB Smear



Suspect Pulmonary TB: AFB Smear and Chest X-ray



Suspect Pulmonary TB: AFB Smear and MTD Probe



Bacteriologic Examination

- Sputum collection – those symptomatic or with abnormal chest x-rays consistent with TB, for AFB smear and culture:
  - A series of three samples
  - Spontaneous or induced
  - At least 8 hrs. apart, and one in early AM
- All specimens should be cultured, regardless of smear result
- Smear/stain results in 1 day, culture results take up to 6-8 weeks
- *M.tb* can be cultured from any body fluid or tissue
- Specimen collected depends on the site of potential disease

MTD - Direct Tests for TB

Mycobacterium tuberculosis direct or TB PCR – results in 1-2 days

- These rapid tests are done directly on raw respiratory samples; culture growth is not needed
- Very sensitive on samples with higher smear positivity
- A negative test does not rule out TB, especially with negative smear results
- A negative does not provide enough evidence to release from isolation

Gene Xpert – results in 6-8 hours

Evaluation

- Medical History
  - Symptoms of TB
  - Exposure to TB, Hx previous TB infection, or Hx TB disease
  - Risk factors for progression to TB disease
- TB skin test or IGRA
- Chest x-ray or CT
- Bacteriologic Examination of sputa, including:
  - Smears (+AFB)
  - MTD or PCR "direct test (RNA based)
  - Culture results "DNA probes" or traditional culture

Diagnosis

- Evaluate all patients with symptoms of TB for TB disease, regardless of the patient's skin test reaction
- 1/4 to 1/3 of all active MTB cases have negative TST at onset of treatment

Symptoms of TB Disease

Pulmonary Symptoms

- Cough
- Pain in the chest when breathing or coughing
- Coughing up sputum or blood

Systemic Symptoms

- Fatigue/malaise
- Decreased appetite
- Unexplained weight loss usually > 10 pounds
- Fever
- Night sweats
- Other symptoms specific to the site of the TB disease

Positive Case – What do I Do?

- Notify the North Dakota Department of Health
- Place in isolation until no longer infectious
  - Repeat sputum smear and culture X 3 weeks
- Contact Investigation
  - How infectious of the person with TB
  - Length of exposure
  - Environment in which transmission occurs
    - Close proximity
    - Indoors, Outdoors
- DOT (Direct Observed Therapy)

Medication to Treat TB

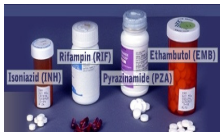
Drugs that could kill TB bacteria were discovered in 1940s and 1950s

- Streptomycin (SM) discovered in 1943
- Isoniazid (INH) and *p*-aminosalicylic acid (PAS) discovered between 1943 and 1952

Treatment

First Line

- Isoniazid*
- Rifampin*
- Ethambutol*
- Pyrazinamide*
- Rifapentine
- Rifabutin



Second Line

- Cycloserine
- Ethionamide
- Levofloxacin
- Moxifloxacin
- Gatifloxacin
- *P*-Aminosalicylic acid
- Streptomycin
- Amikacin/kanamycin
- Capreomycin
- Linezolid

Length of Treatment

- 6 – 9 months
- DOT (Direct Observed Therapy)
- Drug resistant TB can take 12 months to years to treat

Drug Resistance

Primary Resistance

- **Caused by person-to-person transmission of drug-resistant organisms**

Secondary Resistance

Develops during TB treatment:

- **Patient was not given appropriate treatment regimen**
- **Patient did not follow treatment regimen as prescribed**

Types of Drug Resistance

- Mono-resistant
  - Resistant to any one TB treatment drug
- Poly-resistant
  - Resistant to at least any 2 TB drugs but not both isoniazid and rifampin
- Multidrug resistant (MDR)
  - Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
- Extensively drug resistant (XDR)
  - Resistant to isoniazid and rifampin, PLUS resistant to any flouoroquinolone and at least 1 or the 3 injectable second-line drugs (amikacin, kanamycin or capriomycin)

Isoniazid—Side Effects

- GI Intolerance
- Nausea, abdominal pain common
- Vomiting less common
- Peripheral neuropathy:
  - dose-related
  - -<0.2% of patients will have -symptoms include:
    - burning, tingling, numbness of fingers/toes (usually toes first)
  - -can be managed by starting/increasing B6
- Rash:
  - -Mild rash or itching
    - ☐pre-medicate with Benadryl

Steps to alleviate side effects:

- Co-administer with food (small snack)
- Reassurance
- Medications (promethazine, pepcid)
- Pre-medicate with antinausea

Isoniazid – Side Effects

- Hepatitis
  - Patients can be asymptomatic
  - Fatigue, nausea, abdominal pain, vomiting common
  - Jaundice
- 10-20% of persons who take isoniazid will develop asymptomatic LFT increase
- In most cases these will resolve with continued treatment
- Not dose-related
- Clinically significant hepatitis occurs in 0.1-1% of patients
- Risk increased with age, ETOH, HIV, concurrent viral hepatitis

Rifampin—Side Effects

- GI side effects
- Orange urine/body fluids (sweat)
  - Harmless but may stain contact lenses, clothing
  - Need to let patients know beforehand

Rifampin—Side Effects

- Hepatitis:
  - Occurs in about 0.6% of patients with rifampin alone
  - Not dose-related
- Isolated cholestasis (increased bilirubin)
- Managed similarly to isoniazid
- Flu-like syndrome:
  - Fevers, myalgias, arthralgias, headache
  - Onset of symptoms usually 1-2 hours after dose, usually resolves within 12 hours of dose

Rifampin

- Increases the metabolism of medications,
  - birth control
  - coumadin
  - methadone
  - glipizide, glimepiride,glyburide
  - levothyroxine
  - protease inhibitors

Pyrazinamide—Side Effects

- GI symptoms
- Arthralgias (joint pain)
- Rash
- Hyperuricemia (elevateduric acid)-may precipitate gout,
- Kidney stones
- TB medications do not usually require discontinuation

Ethambutol – Side Effects

- Optic neuritis:
  - blurred vision
  - "spots" in patient's field of vision
  - red/green color blindness
  - Dose-related
    - Drug should be discontinued
    - Usually reversible if stopped right away

Prevention of Optic Neuritis

- Monitor vision
- Improve diabetic control
- Multivitamin (B complex, Folate)

Progression to TB Disease

- Risk of developing TB disease is highest the first 2 years after infection
- People with LTBI can be given treatment to prevent them from developing TB disease
- Detecting TB infection early and providing treatment helps prevent new cases of TB disease

Increase in TB in mid 1980s

- Contributing factors:
  - Inadequate funding for TB control programs
  - HIV epidemic
  - Increased immigration from countries where TB is common
  - Spread in homeless shelters and correctional facilities
  - Increase and spread of multidrug-resistant TB

TB/HIV Co-Infection

In an HIV-infected person, TB can develop in one of two ways:

- Person with LTBI becomes infected with HIV and then develops TB disease as the immune system is weakened
- Person with HIV infection becomes infected with M. *tuberculosis* and then rapidly develops TB disease

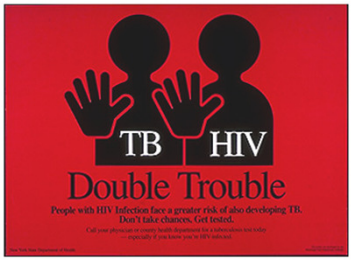
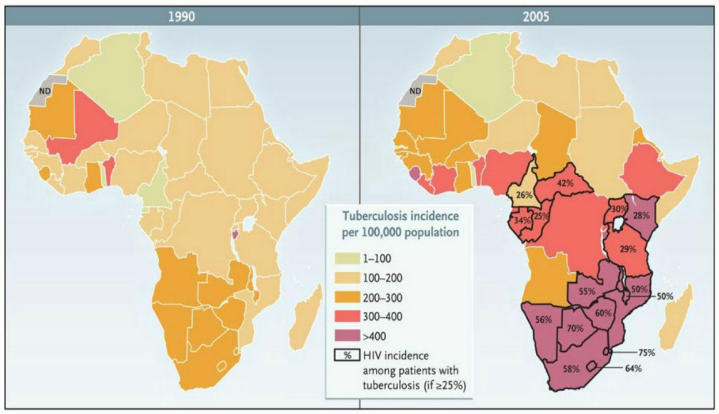


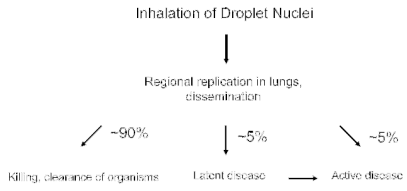
Image credit: Mississippi State Department of Health

TB is the leading killer of people who are HIV infected

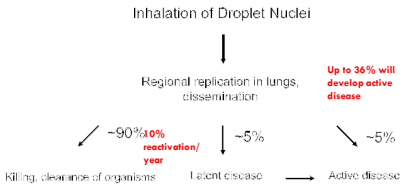


Outcome of Exposure to TB

Without HIV



With HIV



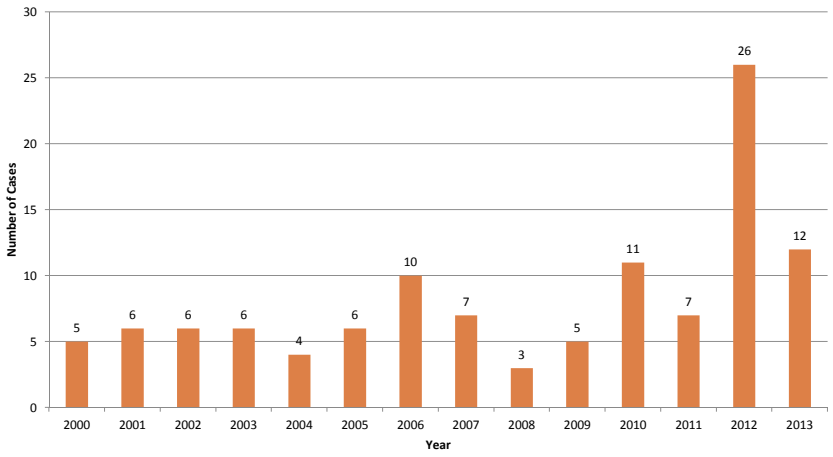
TB Prevention

- Early detection
- If LTBI, take medication to treat the infection
- Education and Screening
- Personal hygiene
- Isolation

Who is at Risk in North Dakota?

- Homeless
- Contacts to known TB cases
- Persons with HIV or other immunosuppressed diseases
- Foreign Born
- Those in conjugate settings

Active TB Cases in North Dakota, 2009 - 2013



Thank you for attending TB 101

Please take post-test to receive CEU's for this presentation, you must score at least 70% to receive credit.

This presentation will be archived and available for review on www.ndhealth.gov/HIV/Resources/resources.htm

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NORTH DAKOTA DEPARTMENT of HEALTH